Conferences and Reviews

Thromboangiitis Obliterans
An Update on Buerger's Disease

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Buerger's disease (thromboangiitis obliterans) is a nonnecrotizing vasculitis affecting small and medium-sized arteries, typically in young male smokers. The diagnosis can often be made on the basis of a careful history and physical examination, together with ancillary laboratory studies. Occasionally arteriography is warranted to confirm the diagnosis. The pathological findings are distinctive and distinguish this disorder from other arterial occlusive diseases. Successful therapy is possible only with absolute abstinence from tobacco.

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Thromboangiitis obliterans (TAO) is an inflammatory, nonatherosclerotic, occlusive disease of small- and medium-sized arteries and veins that involves distal vessels of the extremities. First described by Felix von Winiwarter in 1879, it was revisited by Leo Buerger, a surgeon at the Mount Sinai Hospital in New York, who presented his paper on thromboangiitis obliterans in 1908.[1] After his presentation, thromboangiitis obliterans became commonly referred to as Buerger's disease.

Some cogent reasons for a current review of Buerger's disease exist. For one, it is important to recognize that a growing number of people with this disease are women, a fact that can most likely be attributed to the increasing prevalence of smoking in young women. It is also important to indicate new therapeutic directions such as prostanoids and therapeutic angiogenesis.

Pathogenesis and Epidemiology

Buerger's disease primarily affects young male smokers; in the past, they represented over 90% of affected people. Recently, however, women have made up an increasing percentage of affected people—more than 20% in some studies.[2,3]

The pathogenesis of the inflammatory process of Buerger's disease is not yet understood. Buerger's 1908 description of thromboangiitis obliterans proposed a multifactorial etiology of the disease, with smoking being an important determinant.[4] Tobacco use clearly plays a major role; the typical patient is a heavy smoker, and the progression of the disease is closely related to the continued use of tobacco. Approximately 40% of Buerger's disease patients who continue to smoke will need to have a digit or extremity amputated, as opposed to 5% of those who abstain from smoking.[2] Moreover, the incidence of Buerger's disease in the US has declined as tobacco use has also declined. At the Mayo Clinic in Rochester, Minnesota, the percentage of diagnosed cases of Buerger's disease has declined from 104.3 per 100,000 patients in 1947 to 12.6 per 100,000 patients in 1986.[5] At the same time, however, the percentage of new cases in women is increasing, which parallels the increased percentage of young women in the US who are smoking.[2,6]

The role of second-hand smoke in the pathogenesis of Buerger's disease has not been seriously examined, although we (and others) have had anecdotal experience suggesting that this possible mechanism should be investigated.[7] It is clear, however, that the use of tobacco is not the only factor in the disease's pathogenesis—Buerger's disease is relatively uncommon, even in heavy smokers. Genetic factors likely play a role. Of note, the prevalence of Buerger's disease is greater in Eastern Europe and Asia than in the US.[8] Some investigators have documented an increased frequency of HLA-A9 and HLA-Bw5 or HLA-B8, B35, and B40 antigens among Eastern European and Asian Buerger's disease patients,[9–11] although this has not been confirmed by others.[12]

There is a growing body of evidence that alterations in autoimmune responses play a role in Buerger's disease. Harkavy was the first to suggest the possibility of hypersensitivity to tobacco antigens in Buerger's disease patients.[13] Cell-mediated sensitivity to types I and III collagen (found in vascular smooth muscle) and circulating antibodies to types I and III collagen and to elastin

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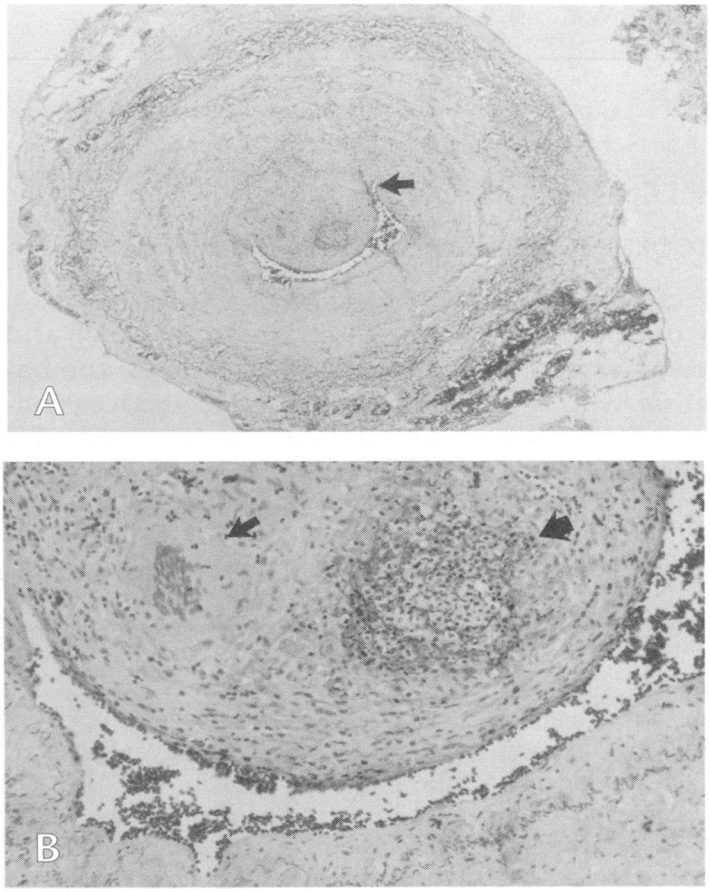

Figure 1.— (A) This is a low-power photomicrograph of a cross-section of the greater saphenous vein. A transmural inflammation is apparent without smooth muscle cell necrosis. A highly cellular thrombus (arrow) occludes most of the lumen. Figure (B) is a high-power photomicrograph of the same cross-section. A highly cellular thrombus occludes much of the lumen. A multinucleate giant cell (arrow) and microabscess (arrowhead) are present within the thrombus.

are detected with significantly greater frequency in patients with Buerger's disease than in patients with atherosclerotic vascular disease.[14,15]

Pathology

Clinical evidence usually is sufficient to establish the diagnosis of Buerger's disease, but histopathology is definitive. Histopathological specimens may be obtained from amputated tissue or from biopsy specimens of a superficial inflamed vein. Biopsy specimens taken from ischemic limbs are contraindicated because of the risk of inducing a nonhealing wound.

The pathological findings Buerger's disease are similar in the involved arteries and veins. The histopathological characteristics are sufficiently distinctive for this disease to have established it as an entity separate from atherosclerosis, idiopathic arterial thrombosis, or necrotizing vasculitides. Unlike cases of necrotizing vasculitides, Buerger's disease involves no necrosis of vascular smooth muscle and no fragmentation of the elastic

TABLE 1.—*Clinical Presentation of Buerger's Disease*

	Author		
	Olin[2]	*Ohta*[12]	*Kaniak*[17]
Number of patients	112	328	124
Mean age (years)	42 (dx)	36(onset)	29(onset)
History, or signs of			
Intermittent claudication	63%	18%	32%
Rest pain	81%	50%	—
Ischemic ulcers	76%	50%	88%
Thrombophlebitis	38%	51%	59%
Raynaud's phenomenon	44%	—	16%
Coldness/cyanosis/paresthesia	69%	11%	—

lamellae. In its acute stages, a panvasculitis is observed with inflammation of the adventitia, media, and intima (Figure 1a). The hallmark of Buerger's disease is an occlusive, highly cellular thrombus with microabscesses and multinucleated giant cells within the thrombus (Figure 1b). This thrombus differs from the bland thrombus seen in hypercoagulable states; in Buerger's disease, segments of vessels may also contain thrombi not infiltrated with inflammatory cells. Segments of involved arteries or veins are interposed between segments of normal vessels, whereas atherosclerosis is characterized by more diffuse arterial involvement. In more advanced stages of Buerger's disease, the lesions become less distinctive, at which time organized and re-canalized thrombi may still exist. They thus provide a focal residual inflammatory reaction sufficient to suggest Buerger's disease.[8]

Clinical Presentation and Diagnosis

The diagnosis of Buerger's disease may be suspected on clinical grounds alone (Tables 1 and 2). Patients with the disease are usually male smokers and between 20 and 40 years old. Other risk factors that are generally

TABLE 2.—*Clinical Distinction Between Atherosclerosis and Buerger's Disease*[34]

Patient Characteristics	*Atherosclerosis*	*Buerger's disease*
Age at presentation	>40	20–40
History of tobacco use	+	++
Other risk factors[a]	+	+/–
Upper extremity involvement	–/+	+
Proximal vessel involvement	++	–/+
Migratory superficial thrombophlebitis	–	+

++ = invariably present; + = usually present; +/– = occasionally present; –/+ = uncommonly present; – = not a feature of the disease

[a] Risk factors for development of atherosclerosis other than tobacco: hyperlipidemia, hypertension, diabetes mellitus, family history of premature stroke or myocardial infarction

TABLE 3.—*Pattern of Arterial Occlusion in Buerger's Disease**

Level of Occlusion	
Infrapopliteal	90–100%
Femoropopliteal	12–40%
Suprainguinal	0–23%
Infracubital	7–63%
Supracubital	0–14%
Number of Limbs Involved	
One limb only	0–39%
Two limbs	17–80%
Three limbs	7–43%
Four limbs	11–40%

* From references 2, 15, 17, 23, 24

associated with atherosclerosis may not be present. Although the incidence of Buerger's disease in young women is increasing, male patients still outnumber female patients.[2,6,16]

Patients most commonly seek medical care for symptoms related to ischemia of distal lower extremities (arch or forefoot claudication, gangrene, rest pain [pain at a resting state], or distal cyanosis). Unlike in cases of atherosclerosis, the upper extremities are often involved. Indeed, up to 90% of Buerger's disease patients will report symptoms of upper extremity ischemia, including Raynaud's phenomenon (usually asymmetrical), cyanosis, gangrene of a digit, or, uncommonly, intermittent claudication of the hand or forearm.[17] Involvement of all four limbs is observed in up to 43% of patients[18] (Table 3). Nonextremity arteries are less commonly affected, although the involvement of coronary, celiac, and cerebral arteries has been described.[19–22]

Patients with Buerger's disease may describe episodes of migratory superficial thrombophlebitis (in the absence of varicose veins) (Figure 2), which usually affects small- or medium-sized veins of the foot, calf, and forearm; less commonly, the lesser or greater saphenous veins; and very rarely, femoral or axillary veins or superficial veins of the trunk. The lesions are usually linear, but sometimes tuberous, especially when located on plantar side of the foot.

Physical examination reveals evidence for occlusive disease of small- and medium-sized vessels. The radial, ulnar, dorsalis pedis, or posterior tibial pulses may be absent. A careful examination, including an Allen's test, will uncover arterial disease of the upper extremity in more than half of the patients examined. In the early stage of the disease, involved vessels are tender and indurated and reflect the local inflammatory reaction. Unlike with atherosclerosis, subclavian or aortoiliac bruits or reduced pulsations of the brachial, femoral, or popliteal arteries are not usually detected.

In a young smoker with an ischemic limb, the diagnosis of Buerger's disease is almost certain when there is (1) occlusive disease of infrapopliteal arteries in the absence of proximal arterial disease; (2) a presence or a history of superficial migratory thrombophlebitis; (3) upper limb arterial involvement; and (4) no other risk factors for atherosclerosis (other than tobacco use).

Laboratory testing helps to exclude other considerations in the differential diagnosis. Antinuclear antibody level, erythrocyte sedimentation rate, rheumatoid factor, VDRL antigen, hepatitis serologies, and serum complement levels (C_1–C_4) can be useful in excluding other causes of vasculitis. In addition to a complete blood count, antithrombin III, antiphospholipid antibodies, factor V Leiden, protein C, and protein S levels as well as prothrombin time and partial thromboplastin time can help to exclude the possibility of hypercoagulopathies, although these disorders are more commonly associated with venous thromboses. Most test results of patients with Buerger's disease are within the normal ranges; however, elevated erythrocyte sedimentation rate, fibrinogen level, and platelet count may occur in patients with an active ulcer or necrosis. Antiphospholipid, antielastin, and anticollagen antibodies may also be found, although the titers are usually low.

The results of noninvasive vascular laboratory studies can be used to confirm and quantify the loca-

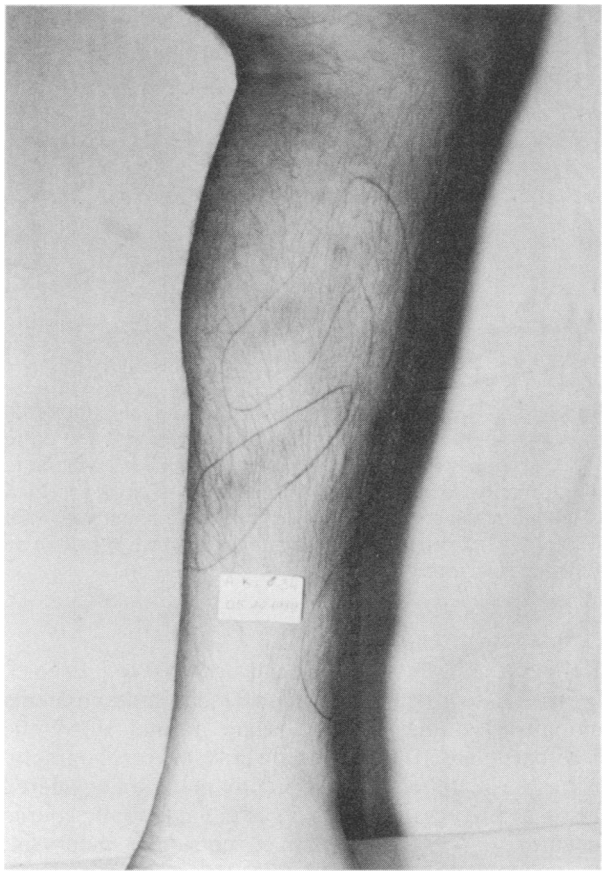

Figure 2.—This photograph shows superficial migratory thrombophlebitis in a patient with thromboangiitis obliterans.

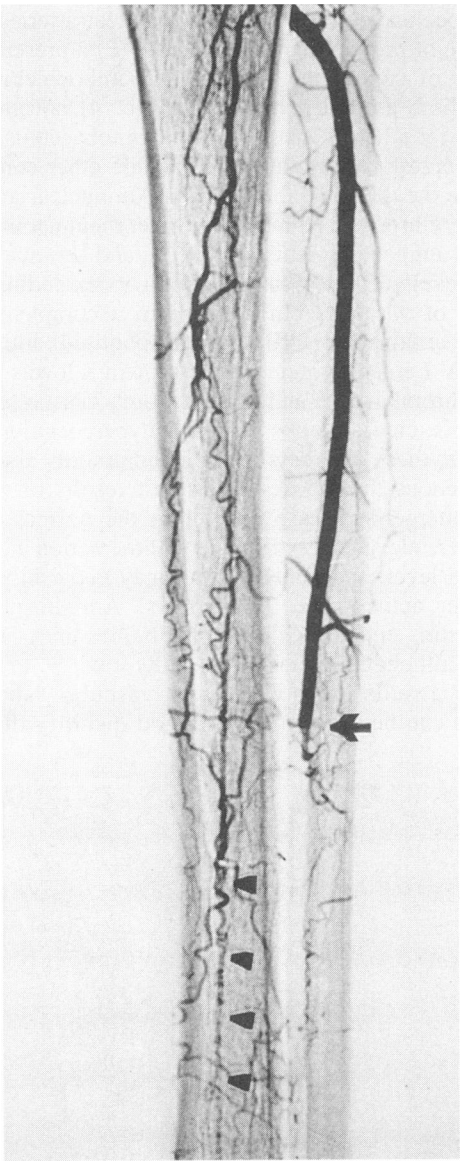

Figure 3.—This photograph is of the digital subtraction angiogram of the left lower extremity. The peroneal and posterior tibial arteries are occluded. The anterior tibial artery occludes abruptly in mid-course (arrow). Numerous cork-screw collaterals are visible, some of these following the course of normal vessels (Martorell's sign; arrowheads indicate the previous course of the posterior tibial artery).

tion and degree of arterial occlusive disease. Typically, segmental arterial pressure measurements and pulse volume recordings are normal above the knee and markedly reduced distally. Ultrasonography of the aorta and echocardiography may be considered in some patients to rule out a proximal embolic source (such as an aortic aneurysm, a ventricular aneurysm, or a valvular abnormality).

TABLE 4.—*Characteristic Angiographic Findings in Buerger's Disease**

1. Multiple, segmental arterial involvement ("skip lesions")	100%
2. Smooth vessel wall in nonaffected arteries	100%
3. Abrupt arterial occlusions	42–100%
4. Smoothly tapered arterial occlusions	40–41%
5. Tortuous or corkscrew type collaterals	100%
6. "Direct" collaterals ("Martorell sign")	80%
7. "Tree root" or "spider's leg" collaterals	40%

* From references 22–24, 35

The history, physical examination, and ancillary laboratory studies of some patients may not provide enough information to confidently establish a diagnosis of Buerger's disease. In such patients, arteriography should be considered. If arteriography is performed for disease of the lower extremities, the infradiaphragmatic aorta should be completely examined to rule out atherosclerotic occlusive or aneurysmal disease of the aorta, which could indicate an embolic source. For the same reasons, an arteriographic examination of the upper extremities should include a complete visualization of the thoracic aorta and great vessels. The arteriographic findings that most characterize Buerger's disease include the following: smooth arterial walls of unaffected arteries, usually proximal to the popliteal and brachial arteries; peripheral, multiple, segmental occlusions, also known as "skip lesions"; and direct "cork-screw" collateral vessels, which follow the course of the thrombosed vessel (Martorell's sign) (Figure 3). These collateral vessels represent the markedly enlarged vasa vasorum of the occluded vessel (Table 4). "Cork-screw" collaterals may be seen in patients with atherosclerosis but are uncommon. Severe infrapopliteal disease in the absence of proximal arterial involvement does not usually occur in atherosclerosis, but it is typical in Buerger's disease.[23–25]

Natural History

The process of Buerger's disease begins in small foot and hand vessels and progresses proximally. Its progression may be *per continuum,* or new lesions may form in a different segment of the arterial tree—known as skip lesions. In most patients, the disease will not extend proximally above the popliteal artery in the legs or the brachial artery in the arms. Collateral circulation is usually poor, and ischemic ulcerations of the toes and fingers develop early in the course of the disease. Ischemia and necrotic changes progress proximally, often necessitating limb amputation.

The disease waxes and wanes, with periods of active disease and acute exacerbation of symptoms alternating

TABLE 5.—*Surgical Revascularisation in Buerger's Disease*[16,26,27]

Author	Number of patients	Years of follow-up	Type of bypass	Patency rate
Shionoya	44	10	Suprainguinal (10)	70%
		7	Femoro-popliteal (10)	60%
		10	Femoro-crural (24)	29%
Izumi	108	5	Aorto-femoral	88%
		5	Infrainguinal	64%
Sasajima	15	4–9	Pedal	60%

with periods of remission. The periods of remission may last many years and not recur if the patient abstains from smoking. Exacerbations are usually related to cigarette smoke exposure. The disease activity is most virulent in the third to fifth decades of life and may be less so in older people (a different temporal pattern than seen in atherosclerosis). Shionoya did not observe any new ulcer formation in his patients older than 60.[16]

Patients with Buerger's disease are severely addicted to cigarette smoking, and most continue to smoke despite their recognition that continued tobacco use will result in severe medical problems. The use of tobacco products in patients with Buerger's disease fulfills the following criteria for drug addiction: compulsive use of the agent despite harmful effects; psychoactive effects of the agent (such as feeling of pleasure, increased alertness); and drug-reinforced behavior (an activity, such as inhaling smoke in this case, that is associated with an effect that is pleasurable or otherwise conducive to maintaining the activity).

Treatment

An understanding of the pathogenesis of Buerger's disease may lead to specific therapy. At present the therapy remains symptomatic. Absolute abstinence from smoking is critical for therapeutic success and favorably affects the prognosis at any stage of the disease.[2,7,17] The patient must be made aware of the dire consequences of continued tobacco use. Unfortunately, many patients continue smoking regardless of the consequences.

The therapeutic goals for Buerger's disease involve

- improving arterial flow to the limb;
- alleviating ischemic pain;
- treating concomitant infections;
- treating thrombophlebitis; and
- improving wound healing by treating locally.

Surgical revascularization is not an option in most cases because of poor run-off. It should thus only be considered in patients with impending amputation and a target vessel.[17] In such cases, it may be possible to salvage the limb with surgery (Table 5).[26,27] The overall success of revascularization depends on the patient's smoking status, and patency rates vary from 29% to 88% with a follow-up of 5 to 10 years (Table 5).

Thrombolytic therapy has not been found to be very helpful, which is most likely due to preexisting organized thrombus and poor run-off.[28] In cases of acute exacerbation, in which presumably fresh thrombus is responsive to thrombolysis, thrombolytic therapy may be attempted with some success.[29]

Lumbar and thoracic sympathectomy are performed to reduce pain, to improve cutaneous flow, and to heal ischemic ulcers.[2,17] Vasodilator therapy is generally not effective, although prostanoids may be useful. In a study involving 133 patients with critical limb ischemia due to thromboangiitis obliterans, Fiessinger and colleagues examined the efficacy of intravenous Iloprost—a stable prostacyclin analog—versus aspirin in the relief of rest pain and healing of ischemic ulcers. Patients were treated for periods of 21 to 28 days. Treatment with aspirin improved pain and ulcer healing in 17% of the patients, whereas treatment with Iloprost improved pain and ulcer healing in 85% of the patients. At six months follow-up, 22% of the patients receiving aspirin and 88% of patients receiving Iloprost were improved.[30] We have observed similar benefits with prostanoid therapy. Prostaglandin E_1 (PGE_1) and Iloprost improve microcirculation in the ischemic leg by virtue of their antiplatelet, cytoprotective, and vasodilatory actions. Prostanoids (such as Iloprost and PGE_1) are now considered in Europe as a first line treatment for patients with critical leg ischemia and Buerger's disease.[31]

Emerging new therapies, especially therapeutic angiogenesis using vascular endothelial growth factor (VEGF) or basic fibroblast growth factor (bFGF)[32,33] may be very useful in the treatment of Buerger's disease. Isner has demonstrated significant improvement in blood flow, symptoms, and wound healing in patients with atherosclerotic critical leg ischemia treated with VEGF gene transfer.[33] We are investigating the efficacy of bFGF in patients with atherosclerotic critical leg ischemia and intermittent claudication.

Severe ischemic pain may be managed with narcotic analgesics or, in some cases, prolonged epidural analgesia. Pain relief will lead to a reduction in cutaneous vasoconstriction and facilitate healing of ulcerations.

An ischemic foot must be protected from thermal and mechanical trauma; approximately half of amputations can be traced to a nonhealing ulcer that came from a preventable injury or from poorly fitting shoes. Local infections should be promptly treated with antibiotics and antifungal agents; they are not recommended, however, for use directly on an open wound. Wounds should be carefully debrided mechanically or enzymatically, and water-based gels should be used to prevent drying. Ointments are not recommended because of poor absorption from the surface of the ischemic wound.

Superficial thrombophlebitis responds to warm compresses and oral nonsteroidal anti-inflammatory drugs (NSAIDs). In more severe cases, topical or systemic steroids may be helpful.

Prognosis

Prognosis of Buerger's disease is directly related to tobacco use. Patients who are able to stop smoking avoid recurrences of the disease and amputations.[7] In those who continue to smoke, the disease will progress and lead to limb loss—often multiple amputations. The successes of various therapies for Buerger's disease are strongly dependent on abstinence from smoking.[2,7]

Buerger's disease rarely involves visceral vessels, so patients with the disease do not appear to be at increased risk of stroke or myocardial infarction (unlike patients with atherosclerosis of the extremities). The mortality rates of patients with Buerger's disease thus may not be higher than those of age- and sex- matched populations.[16,34,35] Multiple amputations and progressive disability cause a dramatic decline in quality of life, however. Our data suggest that people with Buerger's disease are prone to premature atherosclerosis, and the incidence of both peripheral and coronary atherosclerosis is higher in this group than in healthy age- and sex-matched populations.[36]

Summary

Buerger's disease (thromboangiitis obliterans), a non-necrotizing vasculitis affecting small- and medium-sized arteries, is typically seen in young male smokers. The diagnosis of Buerger's disease can often be made on the basis of a careful history and physical examination, together with ancillary laboratory studies. Occasionally arteriography is warranted to confirm the diagnosis. The pathological findings are distinctive and distinguish this disorder from other arterial occlusive diseases. Most importantly, successful therapy is possible only with absolute abstinence from tobacco.

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